Office Action Dated: March 31, 2004

PATENT REPLY FILED UNDER EXPEDITED PROCEDURE PURSUANT TO 37 CFR § 1.116

This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims:

1. (Previously Presented): A compound, comprising: a targeting moiety and a chelator, wherein the targeting moiety is bound to the chelator, is a peptide or peptidomimetic, and binds to a receptor that is upregulated during angiogenesis, the receptor is $\alpha_v \beta_3$, and the compound has a linking group between the targeting moiety and chelator, the linking group having the formula:

$$(CR^6R^7)_g$$
- $(W)_h$ - $(CR^{6a}R^{7a})_g$ '- $(Z)_k$ - $(W)_h$ '- $(CR^8R^9)_g$ "- $(W)_h$ "- $(CR^{8a}R^{9a})_g$ "

wherein,

W is independently selected at each occurrence from the group: O, S, NH, NHC(=O), C(=O)NH, C(=O), C(=O)O, OC(=O), NHC(=S)NH, NHC(=O)NH, SO₂, (OCH₂CH₂O)_s, (CH₂CH₂O)_s, (OCH₂CH₂CH₂O)_t, and (aa)_t;

aa is independently at each occurrence an amino acid;

- Z is selected from the group: aryl substituted with 0-3 R¹⁰, C₃₋₁₀ cycloalkyl substituted with 0-3 R¹⁰, and a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O and substituted with 0-3 R¹⁰;
- R^6 , R^{6a} , R^7 , R^{7a} , R^8 , R^{8a} , R^9 and R^{9a} are independently selected at each occurrence from the group: H, =O, COOH, SO₃H, PO₃H, C₁ C₅ alkyl substituted with 0-3 R^{10} , aryl substituted with 0-3 R^{10} , benzyl substituted with 0-3 R^{10} , and C₁ C₅ alkoxy substituted with 0-3 R^{10} , NHC(=O) R^{11} , C(=O)NH R^{11} , NHC(=O)NH R^{11} , NHC(=O)NH R^{11} , and a bond to the chelator;
- R¹⁰ is independently selected at each occurrence from the group: a bond to the chelator, COOR¹¹, OH, NHR¹¹, SO₃H, PO₃H, aryl substituted with 0-3 R¹¹, C₁₋₅ alkyl

Office Action Dated: March 31, 2004

PATENT REPLY FILED UNDER EXPEDITED PROCEDURE PURSUANT TO 37 CFR § 1.116

substituted with 0-1 R^{12} , C_{1-5} alkoxy substituted with 0-1 R^{12} , and a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O and substituted with 0-3 R^{11} ;

R¹¹ is independently selected at each occurrence from the group: H, aryl substituted with 0-1 R¹², a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O and substituted with 0-1 R¹², C ₃₋₁₀ cycloalkyl substituted with 0-1 R¹², polyalkylene glycol substituted with 01 R¹², carbohydrate substituted with 0-1 R¹², cyclodextrin substituted with 0-1 R¹², amino acid substituted with 0-1 R¹², polycarboxyalkyl substituted with 0-1 R¹², polyazaalkyl substituted with 0-1 R¹², peptide substituted with 0-1 R¹², wherein the peptide is comprised of 2-10 amino acids, and a bond to the chelator;

R¹² is a bond to the chelator:

```
k is selected from 0, 1, and 2;
h is selected from 0, 1, and 2;
h' is selected from 0, 1, 2, 3, 4, and 5;
h" is selected from 0, 1, 2, 3, 4, and 5;
g is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;
g' is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;
g" is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;
g" is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;
s' is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;
s' is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;
s' is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;
t is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;
with the proviso that at least one of k, h, h', h", g, g', g", and g"' is other than 0.
```

- 2. (Previously Presented): A compound according to Claim 1, wherein the targeting moiety is a peptide or a mimetic thereof and the linking group is present between the targeting moiety and chelator.
- 3. (Previously Presented): A compound according to Claim 2, the compound is of the formula:

$$(Q)_d$$
- L_n - C_h or $(Q)_d$ - L_n - $(C_h)_{d'}$

wherein, Q is a peptide independently selected from the group:

- K is an L-amino acid independently selected at each occurrence from the group: arginine, citrulline, N-methylarginine, lysine, homolysine, 2-aminoethylcysteine, δ -N-2-imidazolinylornithine, δ -N-benzylcarbamoylornithine, and β -2-benzimidazolylacetyl-1,2-diaminopropionic acid;
- K' is a-D amino acid independently selected at each occurrence from the group: arginine, citrulline, N-methylarginine, lysine, homolysine, 2-aminoethylcysteine, δ -N-2-imidazolinylornithine, δ -N-benzylcarbamoylornithine, and β -2-benzimidazolylacetyl-1, 2-diaminopropionic acid;
- L is independently selected at each occurrence from the group: glycine, L-alanine, and D-alanine;

M is L-aspartic acid;

M' is D-aspartic acid;

Office Action Dated: March 31, 2004

PATENT REPLY FILED UNDER EXPEDITED PROCEDURE PURSUANT TO 37 CFR § 1.116

- R¹ is an amino acid substituted with 0-1 bonds to L_n, independently selected at each occurrence from the group: glycine, L-valine, D-valine, alanine, leucine, isoleucine, norleucine, 2-aminobutyric acid, 2-aminohexanoic acid, tyrosine, phenylalanine, thienylalanine, phenylglycine, cyclohexylalanine, homophenylalanine, 1-naphthylalanine, lysine, serine, ornithine, 1,2-diaminobutyric acid, 1,2-diaminopropionic acid, cysteine, penicillamine, and methionine;
- R² is an amino acid, substituted with 0-1 bonds to L_n, independently selected at each occurrence from the group: glycine, valine, alanine, leucine, isoleucine, norleucine, 2 aminobutyric acid, 2-aminohexanoic acid, tyrosine, L-phenylalanine, D-phenylalanine, thienylalanine, phenylglycine, biphenylglycine, cyclohexylalanine, homophenylalanine, L-1-naphthylalanine, D-1-naphthylalanine, lysine, serine, ornithine, 1,2-diaminobutyric acid, 1,2-diaminopropionic acid, cysteine, penicillamine, methionine, and 2-aminothiazole-4-acetic acid;
- R³ is an amino acid, substituted with 0-1 bonds to Ln, independently selected at each occurrence from the group: glycine, D-valine, D-alanine, D-leucine, D-isoleucine, D-norleucine, D-2-aminobutyric acid, D-2-aminohexanoic acid, D-tyrosine, D-phenylalanine, D-thienylalanine, D-phenylglycine, D-cyclohexylalanine, D-homophenylalanine, D-1-naphthylalanine, D-lysine, D-serine, D-ornithine, D-1,2-diaminobutyric acid, D-1,2-diaminopropionic acid, D-cysteine, D-penicillamine, and D-methionine;
- R⁴ is an amino acid, substituted with 0-1 bonds to L_n, independently selected at each occurrence from the group: glycine, D-valine, D-alanine, D-leucine, D-isoleucine, D-norleucine, D-2-aminobutyric acid, D-2-aminohexanoic acid, D-tyrosine, D-phenylalanine, D-thienylalanine, D-phenylglycine, D-cyclohexylalanine, D-homophenylalanine, D-1-naphthylalanine, D-lysine, D-serine, D-ornithine, D-1,2-diaminobutyric acid, D-1,2-diaminopropionic acid, D-cysteine, D-penicillamine, D-methionine, and 2-aminothiazole-4-acetic acid;

Office Action Dated: March 31, 2004

PATENT REPLY FILED UNDER EXPEDITED PROCEDURE PURSUANT TO 37 CFR § 1.116

R⁵ is an amino acid, substituted with 0-1 bonds to L_n, independently selected at each occurrence from the group: glycine, L-valine, L-alanine, L-leucine, L-isoleucine, L-norleucine, L-2-aminobutyric acid, L-2-aminohexanoic acid, L-tyrosine, L-phenylalanine, L-thienylalanine, L-phenylglycine, L-cyclohexylalanine, L-homophenylalanine, L-1-naphthylalanine, L-lysine, L-serine, L-ornithine, L-1,2-diaminobutyric acid, L-1,2-diaminopropionic acid, L-cysteine, L-penicillamine, L-methionine, and 2-aminothiazole-4-acetic acid;

provided that one of R¹, R², R³, R⁴, and R⁵ in each Q is substituted with a bond to L_n, further provided that when R² is 2-aminothiazole-4-acetic acid, K is N-methylarginine, further provided that when R⁴ is 2-aminothiazole-4-acetic acid, K and K' are N-methylarginine, and still further provided that when R⁵ is 2-aminothiazole-4-acetic acid, K' is N-methylarginine;

d is selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

 L_n is a linking group having the formula:

$$(CR^{6}R^{7})_{g}$$
- $(W)_{h}$ - $(CR^{6a}R^{7a})g'$ - $(Z)_{k}$ - $(W)_{h'}$ - $(CR^{8}R^{9})_{g''}$ - $(W)_{h''}$ - $(CR^{8a}R^{9a})_{g''}$

provided that g+h+g'+k+h'+g"+h"+g" is other than 0;

W is independently selected at each occurrence from the group: O, S, NH, NHC(=O), C(=O)NH, C(=O), C(=O)O, OC(=O), NHC(=S)NH, NHC(=O)NH, SO₂, (OCH₂CH₂O)_s, (CH₂CH₂O)_s, (OCH₂CH₂CH₂O)_s, and (aa)_t;

aa is independently at each occurrence an amino acid;

- Z is selected from the group: aryl substituted with 0-3 R^{10} , C_{3-10} cycloalkyl substituted with 0-3 R^{10} , and a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O and substituted with 0-3 R^{10} ;
- R^6 , R^{6a} , R^7 , R^{7a} , R^8 , R^{8a} , R^9 and R^{9a} are independently selected at each occurrence from the group: H, =O, COOH, SO₃H, PO₃H, C₁ C₅ alkyl substituted with 0-3 R^{10} , aryl substituted with 0-3 R^{10} , benzyl substituted with 0-3 R^{10} , and C₁ C₅ alkoxy substituted with 0-3 R^{10} , NHC(=O) R^{11} , C(=O)NH R^{11} , NHC(=O)NH R^{11} , NHC(1, NH R^{11} , R, and a bond to C_h;
- R¹⁰ is independently selected at each occurrence from the group: a bond to C_h, COOR¹¹, OH, NHR¹¹, SO₃H, PO₃H, aryl substituted with 0-3 R¹¹, C₁₋₅ alkyl substituted with 0-1 R¹², C₁₋₅ alkoxy substituted with 0-1 R¹², and a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O and substituted with 0-3 R¹¹;
- R¹¹ is independently selected at each occurrence from the group: H, aryl substituted with 0-1 R¹², a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O and substituted with 0-1 R¹², C ₃₋₁₀ cycloalkyl substituted with 0-1 R¹², polyalkylene glycol substituted with 01 R¹², carbohydrate substituted with 0-1 R¹², cyclodextrin substituted with 0-1 R¹², amino acid substituted with 0-1 R¹², polycarboxyalkyl substituted with 0-1 R¹², polyazaalkyl substituted with 0-1 R¹², peptide substituted with 0-1 R¹², wherein the peptide is comprised of 2-10 amino acids, and a bond to C_h;

R¹² is a bond to C_h;

k is selected from 0, 1, and 2;

h is selected from 0, 1, and 2;

h' is selected from 0, 1, 2, 3, 4, and 5;

h" is selected from 0, 1, 2, 3, 4, and 5;

Office Action Dated: March 31, 2004

g is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10; g' is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10; g" is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10; g"' is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10; s is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10; s' is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10; s" is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10; t is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10; t' is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

Ch is a metal bonding unit having a formula selected from the group:

$$A^{1} \qquad \qquad A^{2} \qquad \qquad A^{2} \qquad \qquad A^{4} \qquad \qquad A^{4} \qquad \qquad A^{5} \qquad \qquad A^{5$$

 A^1 , A^2 , A^3 , A^4 , A^5 , A^6 , A^7 , and A^8 are independently selected at each occurrence from the group N, NR¹³, NR¹³R¹⁴, S, SH, S(Pg), O, OH, PR¹³, PR¹³R¹⁴, P(O)R¹⁵R¹⁶, and a bond to L_n;

E is a bond, CH, or a spacer group independently selected at each occurrence from the group: C_1 - C_{10} alkyl substituted with 0-3 R^{17} , aryl substituted with 0-3 R^{17} , C_{3-10} cycloalkyl

DOCKET NO.: BMS-0650

Application No.: 09/281,474

Office Action Dated: March 31, 2004

PATENT

REPLY FILED UNDER EXPEDITED

PROCEDURE PURSUANT TO

37 CFR § 1.116

substituted with 0-3 R^{17} , heterocyclo C_{1-10} alkyl substituted with 0-3 R^{17} , wherein the heterocyclo group is a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O, $C_{6\,10}$ aryl $C_{1\,10}$ alkyl substituted with 0-3 R^{17} , $C_{1\,10}$ alkyl $C_{6\,10}$ aryl substituted with 0-3 R^{17} , and a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O and substituted with 0-3 R^{17} ;

 R^{13} , and R^{14} are each independently selected from the group: a bond to L_n , hydrogen, C_1 - C_{10} alkyl substituted with 0-3 R^{17} , aryl substituted with 0-3 R^{17} , C_{1-10} cycloalkyl substituted with 0-3 R^{17} , heterocyclo C_{1-10} alkyl substituted with 0-3 R^{17} , wherein the heterocyclo group is a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O, C_{6-10} aryl C_{1-10} alkyl substituted with 0-3 R^{17} , C_{1-10} alkyl C_{6-10} aryl substituted with 0-3 R^{17} , a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O and substituted with 0-3 R^{17} , and an electron, provided that when one of R^{13} or R^{14} is an electron, then the other is also an electron;

alternatively, R^{13} and R^{14} combine to form = $C(R^{20})(R^{21})$;

 R^{15} and R^{16} are each independently selected from the group: a bond to L_n , OH, C_1 - C_{10} alkyl substituted with 0-3 R^{17} , aryl substituted with 0-3 R^{17} , C_{3-10} cycloalkyl substituted with 0-3 R^{17} , heterocyclo C_{1-10} alkyl substituted with 0-3 R^{17} , wherein the heterocyclo group is a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O, C_{6-10} aryl C_{1-10} alkyl substituted with 0-3 R^{17} , C_{1-10} alkyl C_{6-10} aryl substituted with 0-3 R^{17} , and a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O and substituted with 0-3 R^{17} ;

 R^{17} is independently selected at each occurrence from the group: a bond to L_n , =0, F, Cl, Br, I, -CF₃, -CN, -CO₂R¹⁸, -C(=0)R¹⁸, -C(=0)N(R¹⁸)₂, -CHO, -CH₂OR¹⁸, -OC(=0)R¹⁸, -OC(=0)N(R¹⁸)₂, -NR^{19C}(=0)R¹⁸, -NR^{19C}(=0)OR^{18a}, Page 9 of 30

Office Action Dated: March 31, 2004

PATENT REPLY FILED UNDER EXPEDITED PROCEDURE PURSUANT TO 37 CFR § 1.116

-NR¹⁹C(=O)N(R¹⁸)₂, -NR¹⁹SO₂N(R¹⁸)₂, -NR¹⁹SO₂R^{18a}, -SO₃H, -SO₂R^{18a}, -SR¹⁸, -S(=O)R^{18a}, -SO₂N(R¹⁸)₂, -N(R¹⁸)₂, -NHC(=S)NHR¹⁸, =NOR¹⁸, NO₂, -C(=O)NHOR¹⁸, -C(=O)NHNR¹⁸R^{18a}, -OCH₂CO₂H, 2-(1 morpholino)ethoxy, C₁-C₅ alkyl, C₂-C₄ alkenyl, C₃-C₆ cycloalkyl, C₃-C₆ cycloalkylmethyl, C₂-C₆ alkoxyalkyl, aryl substituted with 0-2 R¹⁸, and a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O;

 R^{18} , R^{18a} , and R^{19} are independently selected at each occurrence from the group: a bond to L_n , H, C_1 - C_6 alkyl, phenyl, benzyl, C_1 - C_6 alkoxy, halide, nitro, cyano, and trifluoromethyl;

Pg is a thiol protecting group;

 R^{20} and R^{21} are independently selected from the group: H, C_1 - C_{10} alkyl, -CN, - CO_2R^{25} , - $C(=O)R^{25}$, - $C(=O)N(R^{25})_2$, C_2 - C_{10} 1-alkene substituted with 0-3 R^{23} , C2-C10 1-alkyne substituted with 0-3 R^{23} , aryl substituted with 0-3 R^{23} , unsaturated 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O and substituted with 0-3 R^{23} , and unsaturated C_{3-10} carbocycle substituted with 0-3 R^{23} ;

alternatively, R²⁰ and R²¹, taken together with the divalent carbon radical to which they are attached form:

$$R^{22}$$

$$R^{23}$$

$$R^{23}$$

$$R^{23}$$

Office Action Dated: March 31, 2004

PATENT REPLY FILED UNDER EXPEDITED PROCEDURE PURSUANT TO 37 CFR § 1.116

- R²² and R²³ are independently selected from the group: H, R²⁴, C₁-C₁₀ alkyl substituted with 0-3 R²⁴, C₂-C₁₀ alkenyl substituted with 0-3 R²⁴, aryl substituted with 0-3 R²⁴, a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O and substituted with 0-3 R²⁴, and C₃₋₁₀ carbocycle substituted with 0-3 R²⁴;
- alternatively, R²², R²³ taken together form a fused aromatic or a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O;

a and b indicate the positions of optional double bonds and n is 0 or 1;

- $R^{24} \text{ is independently selected at each occurrence from the group: } = O, F, Cl, Br, I, -CF_3, -CN, \\ -CO_2R^{25}, -C(=O)R^{25}, -C(=O)N(R^{25})_2, -N(R^{25})_3+, -CH_2OR^{25}, -OC(=O)R^{25}, \\ -OC(=O)OR^{25a}, -OR^{25}, -OC(=O)N(R^{25})_2, -NR^{26}C(=O)R^{25}, -NR^{26}C(=O)OR^{25a}, \\ -NR^{26}C(=O)N(R^{25})_2, -NR^{26}SO_2N(R^{25})_2, -NR^{26}SO_2R^{25a}, -SO_3H, -SO_2R^{25a}, -SR^{25}, \\ -S(=O)R^{25a}, -SO_2N(R^{25})_2, -N(R^{25})_2, =NOR^{25}, -C(=O)NHOR^{25}, -OCH_2CO_2H, and 2-(1-morpholino)ethoxy; and,$
- R^{25} , R^{25a} , and R^{26} are each independently selected at each occurrence from the group: hydrogen and C_1 - C_6 alkyl;

and a pharmaceutically acceptable salt thereof.

4. (Previously Presented): A compound according to Claim 3, wherein:

L is glycine;

R¹ is an amino acid, optionally substituted with a bond to Ln, independently selected at each occurrence from the group: L-valine, D-valine, alanine, leucine, isoleucine, norleucine, 2-aminobutyric acid, tyrosine, phenylalanine, phenylglycine,

Office Action Dated: March 31, 2004

PATENT REPLY FILED UNDER EXPEDITED PROCEDURE PURSUANT TO 37 CFR § 1.116

cyclohexylalanine, homophenylalanine, lysine, ornithine, 1,2-diaminobutyric acid, and 1,2-diaminopropionic acid;

- R² is an amino acid, optionally substituted with a bond to Ln, independently selected at each occurrence from the group: valine, alanine, leucine, isoleucine, norleucine, 2-aminobutyric acid, tyrosine, L-phenylalanine, D-phenylalanine, thienylalanine, phenylglycine, biphenylglycine, cyclohexylalanine, homophenylalanine, L-1-naphthylalanine, D-1-naphthylalanine, lysine, ornithine, 1,2-diaminobutyric acid, 1,2-diaminopropionic acid, and 2-aminothiazole-4-acetic acid;
- R³ is an amino acid, optionally substituted with a bond to Ln, independently selected at each occurrence from the group: D-valine, D-alanine, D-leucine, D-isoleucine, D-norleucine, D-2-aminobutyric acid, D-tyrosine, D-phenylalanine, D-phenylalanine, D-phenylalanine, D-cornithine, D-1,2-diaminobutyric acid, and D-1,2-diaminopropionic acid;
- R⁴ is an amino acid, optionally substituted with a bond to L_n, independently selected at each occurrence from the group: D-valine, D-alanine, D-leucine, D-isoleucine, D-norleucine, D-2-aminobutyric acid, D-tyrosine, D-phenylalanine, D-thienylalanine, D-phenylglycine, D-cyclohexylalanine, D-homophenylalanine, D-1-naphthylalanine, D-lysine, D-ornithine, D1,2-diaminobutyric acid, D-1,2-diaminopropionic acid, and 2-aminothiazole4-acetic acid;
- R⁵ is an amino acid, optionally substituted with a bond to L_n, independently selected at each occurrence from the group: L-valine, L-alanine, L-leucine, L-isoleucine, L-norleucine, L-2-aminobutyric acid, L-tyrosine, L-phenylalanine, L-thienylalanine, L-phenylglycine, L-cyclohexylalanine, L-homophenylalanine, L-1-naphthylalanine, L-lysine, L-ornithine, L-1,2-diaminobutyric acid, L-1,2-diaminopropionic acid, and 2-aminothiazole-4-acetic acid;

d is selected from 1, 2, and 3;

Office Action Dated: March 31, 2004

- W is independently selected at each occurrence from the group: O, NH, NHC(=O), C(=O)NH, C(=O), C(=O)O, OC(=O), NHC(=S)NH, NHC(=O)NH, SO₂, (OCH₂CH₂)_s, (CH₂CH₂O)_s, (OCH₂CH₂CH₂)_s, and (CH₂CH₂CH₂O)_t,
- Z is selected from the group: aryl substituted with 0-1 R¹⁰, C_{3 10} cycloalkyl substituted with 0-1 R¹⁰, and a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O and substituted with 0-1 R¹⁰;
- R^6 , R^{6a} , R^7 , R^{7a} , R^8 , R^{8a} , R^9 , and R^{9a} are independently selected at each occurrence from the group: H, =O, COOH, SO₃H, C₁-C₅ alkyl substituted with 0-1 R^{10} , aryl substituted with 0-1 R^{10} , benzyl substituted with 0-1 R^{10} , and C_1 -C₅ alkoxy substituted with 0-1 R^{10} , NHC(=O) R^{11} , C(=O)NH R^{11} , NHC(=O)NH R^{11} , NHC(=O)NH R^{11} , and a bond to C_h;
- R¹⁰ is independently selected at each occurrence from the group: COOR¹¹, OH, NHR¹¹, SO₃H, aryl substituted with 0-1 R¹¹, a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O and substituted with 0-1 R¹¹, C₁-C₅ alkyl substituted with 0-1 R¹², C₁-C₅ alkoxy substituted with 0-1 R¹², and a bond to C_h;
- R¹¹ is independently selected at each occurrence from the group: H, aryl substituted with 0-1 R¹², a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O and substituted with 0-1 R¹², polyalkylene glycol substituted with 0-1 R¹², carbohydrate substituted with 0-1 R¹², cyclodextrin substituted with 0-1 R¹², amino acid substituted with 0-1 R¹², and a bond to C_h;

```
k is 0 or 1;
h is 0 or 1;
h' is 0 or 1;
s is selected from 0, 1, 2, 3, 4, and 5;
s' is selected from 0, 1, 2, 3, 4, and 5;
```

Office Action Dated: March 31, 2004

s" is selected from 0, 1, 2, 3, 4, and 5; t is selected from 0, 1, 2, 3, 4, and 5;

- A^1 , A^2 , A^3 , A^4 , A^5 , A^6 , A^7 , and A^8 are independently selected at each occurrence from the group: NR^{13} , $NR^{13}R^{14}$, S, SH, S(Pg), OH, and a bond to L_n ;
- E is a bond, CH, or a spacer group independently selected at each occurrence from the group: C₁-C₁₀ alkyl substituted with 0-3 R¹⁷, aryl substituted with 0-3 R¹⁷, C₃₋₁₀ cycloalkyl substituted with 0-3 R¹⁷, and a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O and substituted with 0-3 R¹⁷;
- R^{13} , and R^{14} are each independently selected from the group: a bond to L_n , hydrogen, C_1 - C_{10} alkyl substituted with 0-3 R^{17} , aryl substituted with 0-3 R^{17} , a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O and substituted with 0-3 R^{17} , and an electron, provided that when one of R^{13} or R^{14} is an electron, then the other is also an electron;

alternatively, R^{13} and R^{14} combine to form = $C(R^{20})(R^{21})$;

- $$\begin{split} R^{17} \text{ is independently selected at each occurrence from the group: a bond to L_n, =0, F, Cl, Br, <math display="block"> I, \quad -CF_3, \quad -CN, \quad -CO_2R^{18}, \quad -C(=O)R^{18}, \quad -C(=O)N(R^{18})_2, \quad -CH_2OR^{18}, \quad -OC(=O)R^{18}, \\ -OC(=O)OR^{18a}, \quad -OR^{18}, \quad -OC(=O)N(R^{18})_2, \quad -NR^{19}C(=O)R^{18}, \quad -NR^{19}C(=O)OR^{18a}, \\ -NR^{19}C(=O)N(R^{18})_2, \quad -NR^{19}SO_2N(R^{18})_2, \quad -NR^{19}SO_2R^{18a}, \quad -SO_3H, \quad -SO_2R^{18a}, \quad -S(=O)R^{18a}, \\ -SO_2N(R^{18})_2, \quad -N(R^{18})_2, \quad -NHC(=S)NHR^{18}, \quad =NOR^{18}, \quad -C(=O)NHNR^{18}R^{18a}, \quad -OCH_2CO_2H, \quad \text{and } 2\text{-}(1\text{-morpholino})\text{ethoxy}; \end{split}$$
- R_{18} , R_{18a} , and R_{19} are independently selected at each occurrence from the group: a bond to L_n , H, and C_1 - C_6 alkyl;
- R^{20} and R^{21} are independently selected from the group: H, C_1 - C_5 alkyl, - CO_2R^{25} , C_2 - C_5 1-alkene substituted with 0-3 R^{23} , C_2 - C_5 1-alkyne substituted with 0-3 R^{23} , aryl Page 14 of 30

substituted with 0-3 R^{23} , and unsaturated 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O and substituted with 0-3 R^{23} ;

alternatively, R²⁰ and R²¹, taken together with the divalent carbon radical to which they are attached form:

$$R^{22}$$

$$R^{23}$$

$$R^{23}$$

$$R^{23}$$

$$R^{23}$$

R²² and R²³ are independently selected from the group: H, and R²⁴;

alternatively, R²², R²³ taken together form a fused aromatic or a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O;

 R^{24} is independently selected at each occurrence from the group: $-CO2R^{25}$, $-C(=O)N(R^{25})2$, $-CH_2OR^{25}$, $-OC(=O)R^{25}$, $-OR^{25}$, $-SO_3H$, $-N(R^{25})2$, and $-OCH_2CO_2H$; and,

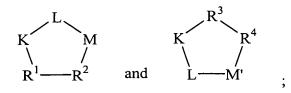
R²⁵ is independently selected at each occurrence from the group: H and C₁-C₃ alkyl.

5. (Previously Presented): A compound according to Claim 4, wherein:

Q is a peptide selected from the group:

Office Action Dated: March 31, 2004

PATENT REPLY FILED UNDER EXPEDITED PROCEDURE PURSUANT TO 37 CFR § 1.116



 R^1 is L-valine, D-valine, D-lysine optionally substituted on the ϵ amino group with a bond to L_n or L-lysine optionally substituted on the ϵ amino group with a bond to L_n ;

 R^2 is L-phenylalanine, D-phenylalanine, D-1-naphthylalanine, 2-aminothiazole-4-acetic acid, L-lysine optionally substituted on the ϵ amino group with a bond to L_n or tyrosine, the tyrosine optionally substituted on the hydroxy group with a bond to L_n ;

 R^3 is D-valine, D-phenylalanine, or L-lysine optionally substituted on the ϵ amino group with a bond to L_n ;

 R^4 is D-phenylalanine, D-tyrosine substituted on the hydroxy group with a bond to L_n , or L-lysine optionally substituted on the ϵ amino group with a bond to L_n ;

provided that one of R^1 and R^2 in each Q is substituted with a bond to L_n , and further provided that when R^2 is 2-aminothiazole-4-acetic acid, K is N methylarginine;

d is 1 or 2;

W is independently selected at each occurrence from the group: NHC(=O), C(=O)NH, C(=O), (CH₂CH₂O)_{s'}, and (CH₂CH₂O)_t;

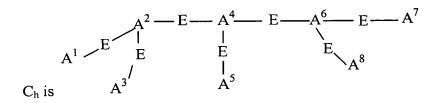
R⁶, R^{6a}, R⁷, R^{7a}, R⁸, R^{8a}, R⁹, and R^{9a} are independently selected at each occurrence from the group: H, NHC(=0)R¹¹, and a bond to C_h;

k is 0;

h" is selected from 0, 1, 2, and 3;

DOCKET NO.: BMS-0650 Application No.: 09/281,474 Office Action Dated: March 31, 2004 PATENT REPLY FILED UNDER EXPEDITED PROCEDURE PURSUANT TO 37 CFR § 1.116

g is selected from 0, 1, 2, 3, 4, and 5; g' is selected from 0, 1, 2, 3, 4, and 5; g" is selected from 0, 1, 2, 3, 4, and 5; g"' is selected from 0, 1, 2, 3, 4, and 5; s' is 1 or 2; t is 1 or 2;



 A^1 is selected from the group: OH, and a bond to L_n ;

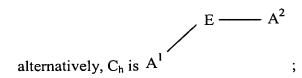
 A^2 , A^4 , and A^6 are each N;

A³, A⁵, and A⁸ are each OH;

 A^7 is a bond to L_n or NH-bond to L_n ;

E is a C_2 alkyl substituted with 0-1 R^{17} ;

 R^{17} is =0;



 A^1 is NH_2 or $N=C(R^{20})(R^{21})$;

E is a bond;

Office Action Dated: March 31, 2004

PATENT REPLY FILED UNDER EXPEDITED PROCEDURE PURSUANT TO 37 CFR § 1.116

A² is NHR¹³;

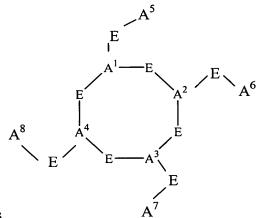
R¹³ is a heterocycle substituted with R¹⁷, the heterocycle being selected from pyridine and pyrimidine;

 R^{17} is selected from a bond to L_n , $C(=O)NHR^{18}$, and $C(=O)R^{18}$;

 R^{18} is a bond to L_n ;

 R^{24} is selected from the group: $CO2R^{25}$, OR^{25} , SO3H, and $N(R^{25})_2$;

R²⁵ is independently selected at each occurrence from the group: hydrogen and methyl;



alternatively, Ch is

 A^1 , A^2 , A^3 , and A^4 are each N;

 A^5 , A^6 , and A^8 are each OH;

 A^7 is a bond to L_n ;

E is a C₂ alkyl substituted with 0-1 R¹⁷; and,

Office Action Dated: March 31, 2004

PATENT REPLY FILED UNDER EXPEDITED PROCEDURE PURSUANT TO 37 CFR § 1.116

 R^{17} is =0.

- 6. (Previously Presented): A compound according to Claim 3, selected from the group:
- (a) cyclo {Arg-Gly-Asp-D-Tyr(N-[2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid]-3-aminopropyl)-Val};
- (b) cyclo {Arg-Gly-Asp-D-Tyr((N-[2-[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid]-18-amino-14-aza-4,7,10-oxy-15-oxo-octadecoyl)-3-aminopropyl)-Val};
- (c) [2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid]-Glu(cyclo{D-Tyr(3-aminopropyl)-Val-Arg-Gly-Asp})-cyclo{D-Tyr(3-aminopropyl)-Val-Arg-Gly-Asp};
- (d) cyclo(Arg-Gly-Asp-D-Tyr-Lys([2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid])};
- (e) cyclo {Arg-Gly-Asp-D-Phe-Lys([2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid])};
- (f) [2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid]-Glu(cyclo{Lys-Arg-Gly-Asp-D-Phe})-cyclo{Lys-Arg-Gly-Asp-D-Phe};
- (g) [2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid]-Phe-Glu(cyclo{Lys-Arg-Gly-Asp-D-Phe})-cyclo{Lys-Arg-Gly-Asp-D-Phe};
- (h) cyclo {Arg-Gly-Asp-D-Nal-Lys([2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid])};

Office Action Dated: March 31, 2004

PATENT REPLY FILED UNDER EXPEDITED PROCEDURE PURSUANT TO 37 CFR § 1.116

- (i) [2-[[[5-[carbonyl]-2-pyridinyl]-hydrazono]methyl]-benzenesulfonic acid]-Glu(cyclo{Lys-Arg-Gly-Asp-D-Nal})-cyclo{Lys-Arg-Gly-Asp-D-Nal};
- (j) cyclo {Arg-Gly-Asp-Lys([2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid])-D-Val};
- (k) [2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid]-Glu(cyclo{Lys-D-Val-Arg-Gly-Asp})-cyclo{Lys-D-Val-Arg-Gly-Asp};
- (l) {cyclo(Arg-D-Val-D-Tyr(N-[2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid]-3-aminopropyl)-D-Asp-Gly};
- (m) cyclo {D-Lys([2-[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid])-D-Phe-D-Asp-Gly-Arg};
- (n) [2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid]-Glu(cyclo{D-Lys-D-Phe-D-Asp-Gly-Arg});
- (o) cyclo {D-Phe-D-Lys([2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid])-D-Asp-Gly-Arg};
- (p) cyclo {N-Me-Arg-Gly-Asp-ATA-D-Lys([2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid])};
- (q) cyclo {Cit-Gly-Asp-D-Phe-Lys([2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid])};
- (r) 2-(1,4,7,10-tetraaza-4,7,10-tris(carboxymethyl)-1-cyclododecyl)acetyl-Glu(cyclo {Lys-Arg-Gly-Asp-D-Phe})-cyclo {Lys-Arg-Gly-Asp-D-Phe};
- (s) cyclo {Arg-Gly-Asp-D-Phe-Lys(DTPA)};

Office Action Dated: March 31, 2004

- (t) cyclo {Arg-Gly-Asp-D-Phe-Lys}2(DTPA);
- (u) Cyclo {Arg-Gly-Asp-D-Tyr(N-DTPA-3-aminopropyl)-Val};
- (v) cyclo {Orn(d-N-2-Imidazolinyl)-Gly-Asp-D-Tyr(N-[2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid]-3-aminopropyl)-Val};
- (w) cyclo {Lys-Gly-Asp-D-Tyr(N-[2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid]-3-aminopropyl)-Val};
- (x) cyclo {Cys(2-aminoethyl)-Gly-Asp-D-Tyr(N-[2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid]-3-aminopropyl)-Val};
- (y) cyclo {HomoLys-Gly-Asp-D-Tyr(N-[2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid]-3-aminopropyl)-Val};
- (z) cyclo {Orn(d-N-Benzylcarbamoyl)-Gly-Asp-D-Tyr(N-[2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid]-3-aminopropyl)-Val};
- (aa) cyclo {Dap(b-(2-benzimidazolylacetyl))-Gly-Asp-D-Tyr(N-[2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid]-3-aminopropyl)-Val};
- (bb) cyclo {Orn(d-N-2-Imidazolinyl)-Gly-Asp-D-Phe-Lys(N-[2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid])};
- (cc) cyclo {Orn(d-N-Benzylcarbamoyl)-Gly-Asp-D-Phe-Lys(N-[2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid])};
- (dd) cyclo {Lys-D-Val-D-Tyr(N-[2-[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid]-3-aminopropyl)-D-Asp-Gly};

 Page 21 of 30

DOCKET NO.: BMS-0650

Application No.: 09/281,474

Office Action Dated: March 31, 2004

PATENT REPLY FILED UNDER EXPEDITED PROCEDURE PURSUANT TO 37 CFR § 1.116

(ee) cyclo {Orn(d-N-Benzylcarbamoyl)-D-Val-D-Tyr(N-[2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid]-3-aminopropyl)-D-Asp-Gly}; and,

(ff) cyclo{Orn(d-N-2-Imidazolinyl)-D-Val-D-Tyr(N-[2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid]-3-aminopropyl)-D-Asp-Gly};

or a pharmaceutically acceptable salt form thereof.

- 7. (Original): A kit comprising a compound of Claim 3, or a pharmaceutically acceptable salt form thereof and a pharmaceutically acceptable carrier.
- 8. (Original): A kit according to Claim 7, wherein the kit further comprises one or more ancillary ligands and a reducing agent.
- 9. (Original): A kit according to Claim 8, wherein the ancillary ligands are tricine and TPPTS.
- 10. (Original): A kit according to Claim 9, wherein the reducing agent is tin(II).
- 11. (Canceled)
- 12. (Previously Presented): A metallopharmaceutical comprising the compound of Claim 1, and a radioisotope selected from the group: ^{99m}Tc, ⁹⁵Tc, ¹¹¹In, ⁶²Cu, ⁶⁴Cu, ⁶⁷Ga, and ⁶⁸Ga, wherein the targeting moiety is a peptide or a mimetic thereof and the linking group is present between the targeting moiety and chelator.
- 13. (Previously Presented): A metallopharmaceutical according to Claim 12, wherein the targeting moiety is a cyclic pentapeptide.

DOCKET NO.: BMS-0650
Application No.: 09/281,474
Office Action Dated: March 31, 2004

PATENT
REPLY FILED UNDER EXPEDITED
PROCEDURE PURSUANT TO
37 CFR § 1.116

- 14. (Previously Presented): A metallopharmaceutical according to Claim 13, wherein the radioisotope is ^{99m}Tc or ⁹⁵Tc, and the metallopharmaceutical further comprises a first ancillary ligand and a second ancillary ligand capable of stabilizing the metallopharmaceutical.
- 15. (Previously Presented): A metallopharmaceutical according to Claim 14, wherein the radioisotope is ^{99m}Tc.
- 16. (Previously Presented): A metallopharmaceutical according to Claim 15, wherein the metallopharmaceutical is selected from the group:
- ^{99m}Tc(tricine)(TPPTS)(cyclo(Arg-Gly-Asp-D-Tyr(N-[[5-[carbonyl]-2-pyridinyl]diazenido]-3-aminopropyl)-Val));
- ^{99m}Tc(tricine)(TPPMS)(cyclo(Arg-D-Val-D-Tyr(N-[[5-[carbonyl]-2-pyridinyl]diazenido]-3-aminopropyl)-D-Asp-Gly));
- ^{99m}Tc(tricine)(TPPDS)(cyclo(Arg-D-Val-D-Tyr(N-[[5-[carbonyl]-2-pyridinyl]diazenido]-3-aminopropyl)-D-Asp-Gly));
- ^{99m}Tc(tricine)(TPPTS)(cyclo(Arg-D-Val-D-Tyr(N-[[5-[carbonyl]-2-pyridinyl]diazenido]-3-aminopropyl)-D-Asp-Gly));
- ^{99m}Tc(tricine)(TPPTS)(cyclo(Arg-Gly-Asp-D-Phe-Lys(N-[[5-[carbonyl]-2-pyridinyl]diazenido])));
- ^{99m}Tc(tricine)(TPPTS)(cyclo(Arg-Gly-Asp-D-Tyr-Lys(N-[[5-[carbonyl]-2-pyridinyl]diazenido])));
- 99mTc(tricine)(TPPTS)([2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid]-Phe-Glu(cyclo{Lys-Arg-Gly-Asp-D-Phe})-cyclo{Lys-Arg-Gly-Asp-D-Phe}); Page 23 of 30

Office Action Dated: March 31, 2004

PATENT REPLY FILED UNDER EXPEDITED PROCEDURE PURSUANT TO 37 CFR § 1.116

- 99mTc(tricine)(TPPTS)(cyclo {Arg-Gly-Asp-D-Nal-Lys([2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid])});
- ^{99m}Tc(tricine)(TPPTS)([2-[[[5-[carbonyl]-2-pyridinyl]-hydrazono]methyl]-benzenesulfonic acid]-Glu(cyclo{Lys-Arg-Gly-Asp-D-Nal})-cyclo{Lys-Arg-Gly-Asp-D-Nal});
- ^{99m}Tc(tricine)(TPPTS)(cyclo(Arg-Gly-Asp-D-Tyr((N-[[5-[carbonyl]-2-pyridinyl]diazenido]-18-amino-14-aza-4,7,10-oxy-15-oxo-octadecoyl)-3-aminopropyl)-Val));
- ^{99m}Tc(tricine)(TPPTS)(N-[[5-[carbonyl]-2-pyridinyl]diazenido]-Glu(O-cyclo(Lys-Arg-Gly-Asp-D-Phe));
- ^{99m}Tc(tricine)(TPPTS)(N-[[5-[carbonyl]-2-pyridinyl]diazenido]-Glu(O-cyclo(D-Tyr(3-aminopropyl)-Val-Arg-Gly-Asp))-O-cyclo(D-Tyr(3-aminopropyl)-Val-Arg-Gly-Asp));
- ^{99m}Tc(tricine)(TPPTS)(cyclo(Arg-Gly-Asp-Lys(N-[[5-[carbonyl]-2-pyridinyl]diazenido])-D-Val));
- ^{99m}Tc(tricine)(TPPTS)(cyclo {D-Lys([2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid])-D-Phe-D-Asp-Gly-Arg});
- 99mTc(tricine)(TPPTS)([2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid]-Glu(cyclo {D-Lys-D-Phe-D-Asp-Gly-Arg})-cyclo {D-Lys-D-Phe-D-Asp-Gly-Arg});
- 99mTc(tricine)(TPPTS)(cyclo {D-Phe-D-Lys([2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid])-D-Asp-Gly-Arg});

Office Action Dated: March 31, 2004

PATENT REPLY FILED UNDER EXPEDITED PROCEDURE PURSUANT TO 37 CFR § 1.116

^{99m}Tc(tricine)(TPPTS)(cyclo(N-Me-Arg-Gly-Asp-ATA-D-Lys(N-[[5-[carbonyl]-2-pyridinyl]diazenido])));

- ^{99m}Tc(tricine)(TPPTS)(cyclo{Cit-Gly-Asp-D-Phe-Lys([2-[[[5-[carbonyl]-2-pyridinyl]hydrazono]methyl]-benzenesulfonic acid])}); and,
- ^{99m}Tc(tricine)(1,2,4-triazole)(cyclo(Arg-Gly-Asp-D-Tyr(N-[[5-[carbonyl]-2-pyridinyl]diazenido]-3-aminopropyl)-Val)).
- 17. (Previously Presented): A metallopharmaceutical according to Claim 13, wherein the radioisotope is ¹¹¹In.
- 18. (Previously Presented): A metallopharmaceutical according to Claim 17, wherein the metallopharmaceutical is selected from the group:

 $(DOTA-^{111}In)-Glu(cyclo \{Lys-Arg-Gly-Asp-D-Phe\})-cyclo \{Lys-Arg-Gly-Asp-D-Phe\};\\ \\ cyclo(Arg-Gly-Asp-D-Phe-Lys(DTPA-^{111}In)); and$

cyclo(Arg-Gly-Asp-D-Phe-Lys)2(DTPA-111In).

- 19. (Previously Presented): A metallopharmaceutical comprising the compound of Claim 1 and a radioisotope selected from the group: ¹⁸⁶Re, ¹⁸⁸Re, ¹⁵³Sm, ¹⁶⁶Ho, ¹⁷⁷Lu, ¹⁴⁹Pm, ⁹⁰Y, ²¹²Bi, ¹⁰³Pd, ¹⁰⁹Pd, ¹⁵⁹Gd, ¹⁴⁰La, ¹⁹⁸Au, ¹⁹⁹Au, ¹⁶⁹Yb, ¹⁷⁵Yb, ¹⁶⁵Dy, ¹⁶⁶Dy, ⁶⁷Cu, ¹⁰⁵Rh, ¹¹¹Ag, and ¹⁹²Ir, the targeting moiety is a peptide or a mimetic thereof and the linking group is present between the targeting moiety and chelator.
- 20. (Previously Presented): A metallopharmaceutical according to Claim 19, wherein the targeting moiety is a cyclic pentapeptide.

PATENT

37 CFR § 1.116

DOCKET NO.: BMS-0650 Application No.: 09/281,474

Office Action Dated: March 31, 2004

- 21. (Previously Presented): A metallopharmaceutical according to Claim 20, wherein the radioisotope is ¹⁵³Sm.
- 22. (Previously Presented): A metallopharmaceutical according to Claim 21, wherein the metallopharmaceutical is selected from the group:

cyclo(Arg-Gly-Asp-D-Phe-Lys(DTPA-153Sm));

cvclo(Arg-Glv-Asp-D-Phe-Lys)2(DTPA-153Sm); and,

cyclo(Arg-Gly-Asp-D-Tyr(N-DTPA(153Sm)-3-aminopropyl)-Val).

- 23. (Previously Presented): A metallopharmaceutical according to Claim 20, wherein the radioisotope is ¹⁷⁷Lu.
- 24. (Previously Presented): A metallopharmaceutical according to Claim 23, wherein the metallopharmaceutical is selected from the group:

cyclo(Arg-Gly-Asp-D-Phe-Lys(DTPA-177Lu));

 $(DOTA-^{177}Lu)-Glu(cyclo\{Lys-Arg-Gly-Asp-D-Phe\})-cyclo\{Lys-Arg-Gly-Asp-D-Phe\};\\$

cyclo(Arg-Gly-Asp-D-Phe-Lys)2(DTPA-177Lu); and

cyclo(Arg-Gly-Asp-D-Tyr(N-DTPA(177Lu)-3-aminopropyl)-Val).

- 25. (Previously Presented): A metallopharmaceutical according to Claim 20, wherein the radioisotope is ⁹⁰Y.
- 26. (Previously Presented): A metallopharmaceutical according to Claim 25, wherein the metallopharmaceutical is:

Office Action Dated: March 31, 2004

PATENT REPLY FILED UNDER EXPEDITED PROCEDURE PURSUANT TO 37 CFR § 1.116

(DOTA-90Y)-Glu(cyclo {Lys-Arg-Gly-Asp-D-Phe})-cyclo {Lys-Arg-Gly-Asp-D-Phe};

- 27. (Previously Presented): A metallopharmaceutical comprising the compound of Claim 1 and, a paramagnetic metal ion selected from the group: Gd(III), Dy(III), Fe(III), and Mn(II), wherein the targeting moiety is a peptide or a mimetic and the linking group is present between the targeting moiety and chelator.
- 28. (Previously Presented): A metallopharmaceutical according to Claim 27, wherein the targeting moiety is a cyclic pentapeptide.
- 29. (Previously Presented): A metallopharmaceutical according to Claim 28, wherein the metal ion is Gd(III).
- 30. (Previously Presented): A metallopharmaceutical according to Claim 29, wherein the contrast agent is:

cyclo(Arg-Gly-Asp-D-Tyr(N-DTPA(Gd(III))-3-aminopropyl)-Val).

- 31. (Previously Presented): A metallopharmaceutical comprising the compound of Claim 1 and a metal selected from the group: Re, Sm, Ho, Lu, Pm, Y, Bi, Pd, Gd, La, Au, Au, Yb, Dy, Cu, Rh, Ag, and Ir, wherein the targeting moiety is a cyclic pentapeptide, and the linking group is present between the targeting moiety and chelator.
- 32. (Previously Presented): A method of treating rheumatoid arthritis in a patient comprising: administering a metallopharmaceutical of Claim 19 capable of localizing in Previously Presented angiogenic vasculature to a patient by injection or infusion.
- 33. (Previously Presented): A method of treating cancer in a patient comprising: administering to a patient in need thereof a metallopharmaceutical of Claim 19 by injection or infusion.

- 34. (Previously Presented): A method of imaging formation of Previously Presented blood vessels in a patient comprising: (1) administering a metallopharmaceutical comprising the compound of Claim 1 and a metal to a patient by injection or infusion;
 (2) imaging the area of the patient wherein the desired formation of Previously Presented blood vessels is located.
- 35. (Previously Presented): A method of imaging cancer in a patient comprising: (1) administering a metallopharmaceutical of Claim 12 to a patient by injection or infusion; (2) imaging the patient using planar or SPECT gamma scintigraphy, or positron emission tomography.

Claims 36-47 (Canceled)

- 48. (Previously Presented): A therapeutic radiopharmaceutical composition, comprising:
 - (a) a metallopharmaceutical of Claim 19; and,
 - (b) a parenterally acceptable carrier.
- 49. (Previously Presented): A diagnostic radiopharmaceutical composition, comprising:
 - (a) a metallopharmaceutical comprising the compound of Claim 1 and a metal; and,
 - (b) a parenterally acceptable carrier.
- 50. (Original): A therapeutic radiopharmaceutical composition, comprising: a radiolabelled targeting moiety, wherein the targeting moiety is a compound Q of Claim 3 and the radiolabel is a therapeutic isotope selected from the group: ³⁵S, ³²P, ¹²⁵I, ¹³¹I, and ²¹¹At.

Claim 51 (Canceled)

Claim 52 (Previously Presented): A compound comprising a peptide or peptidomimetic $\alpha_{\nu}\beta_{3}$ receptor targeting moiety bound to a chelator.